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(54) Title: LUBRICIOUS SELF–STANDING (INTACT) GEL FOR ORAL DELIVERY OF BIOLOGICALLY–ACTIVE INGREDIENTS

(57) Abstract

The present invention relates to a composition comprising–gellan gum, water and a biologically–active ingredient for subsequent providing to and release of said ingredient, active metabolite thereof and/or active derivative thereof or mixtures thereof and the like in a human or animal from a self–lubricated, free–standing gel via effective administration thereto.

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LUBRICIOUS SELF-STANDING (INTACT) GEL FOR ORAL DELIVERY OF BIOLOGICALLY-ACTIVE INGREDIENTS

The present invention relates to a self-standing (intact) lubricious (self-lubricating) hydrogel composition comprising gellan gum and a biologically-active medicinal ingredient. This invention also relates to a process for preparing such a composition comprising gellan gum for subsequent release in a human or animal whereby a therapeutically effective amount of the biologically-active ingredient is provided to and delivered via any one of oral, vaginal and rectal administration in an effective useable manner to the recipient (patient).

BACKGROUND OF THE INVENTION

Sometimes it has been difficult to administer oral medicine to persons who have difficulty swallowing pills like children, elderly persons, paralyzed persons and heart attack and stroke victims. Some patients cannot eat from a bowl and spoon or have psychological or physical difficulty swallowing whole pills. Patients weakened by disease and radiation therapy may have trouble taking pills. Some drug forms cannot or should not be chewed. Pediatric and geriatric patients do not like to take pills. Sometimes hospitals crush pills whereby the pill powder is put into a paper or plastic medication cup and a suspending vehicle, such as orange juice, apricot juice, applesauce, honey or baby food, is added. However care must be taken when crushing medications as one medicament could easily become mixed with another medication. In all instances, the patient must get the full dosage prescribed.

Underdosing a patient can happen when a patient does not get all of his/her does of an active therapeutic agent. This underdosing fails to provide the response sought by the physician. Overdosing can result in adverse reactions that could be detrimental to the patient. Slow and uncertain response time for the onset of an observable reaction to a drug in pill form when taken orally makes it difficult to determine when a proper dose for a particular patient has been administered; the physician may not learn for an hour whether the patient was underdosed or overdosed.

Compliance, which is providing the right amount of medication at the appropriate intervals, is extremely important to medical personnel and patients.

Injections can sometimes be given to avoid using oral routes of administration. But injecting a drug (generally intravenously or intramuscularly) can result in rapid entry of the drug into the patient's bloodstream. Injection changes the removal rate of the drug from the body because the drug is not delivered to the body's liver at the same rate as with a pill. And injections are not for everyone. Sometimes injections can cause psychological stress and worsen a patient's debilitated condition so that injections may be undesirable in such situations.

This invention provides an alternative to the use of pills and pill-crushing techniques and injections for administering determined (known) therapeutic amounts of medication to patients by the use of a self-standing (intact) lubricious gel containing a determined (known) therapeutic amount of medication for the patient.

A. M. Bhakoo, S. Woerly and R. Duncan, *Release of Antibiotics and Antitumour Agents From Alginate and Gellan Gum Gels,* Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 18 (1991), Controlled Release Society, Inc., describes hydrogels which have been developed as controlled release matrices for pharmaceutically active chemicals. This references discloses that alginate (high M or high G) and gellan gum gels were firstly prepared and then loaded with drugs (adriamycin, theophylline, ampicillin, amoxicillin, tetracycline and erthromycin) by imbition over a period of 24 hours and the degree of entrapment, not known prior to gel formation, was thereafter determined.

WPO9402029-A1 discloses an article of manufacture which consists of a spongy matrix whose pores are controlled to size and or distribution and which is made from a co-processed mixture comprising (a) glucomannan and (b) at least one other aqueous gel forming polysaccharide. However, no process appears to be provided for incorporating drugs or minerals, vitamins or supplements, or therapeutic agents or other biologically-active ingredients in such gels.

Japanese Patent Application 89-0724239, "Transparent Gel-Like Composition", discloses a 0.1-1.3 wt. % high-MW polysaccharide based on the total amount of a composition that is added to water and the mixture is heated (e.g., at 90° C), stirred, dissolved and then cooled (e.g., at about 50° C) whereby a volatile substance selected from perfumes, deodorants, mothproofing agents, insecticides and repellents, a proper amount of a surface active agent (e.g., nonionic substance) for solubilization and, if necessary, an anti-freezing agent (e.g., polyhydric alcohol) and an antiseptic agent are added therefore and the mixture is furthermore stirred, left for cooling (e.g., to about 40° C), filled in a container and furthermore left for cooling to room temperature to obtain the composition.

Japanese Patent Application 87-126943, "Heat-Resistant Water-based Gel", discloses that an aqueous suspension of gellan gum is heated at about 95° C above the solution-forming temperature to obtain a homogeneous aqueous solution, to the solution is added an acid (e.g., citric acid, fruit juice, etc.) and calcium chloride, etc., and the solution is reportedly gelatinized by cooling below the gelling temperature to obtain the objective heat resistant water-based gel.

Japanese Patent Application 87-126942, "Gelation of Gellan Gum", discloses a mixture of water and gellan gum which is reported to be a kind of polysaccharide which is produced beforehand and heated at about 85° C which is a solution-forming temperature of gellan gum. The produced aqueous solution of gellan gum is added with an acid (e.g., citric acid, fruit juice) and the mixture is cooled below the gelatinization temperature to effect the gelatinization of the solution and obtain the objective aqueous gel of gellan gum. The amount of the acid is preferably about 15% of the gellan gum.

Japanese Patent Application 88-309150, "Production of Instant Gelatinous Substance", discloses compositions of gellan gum dissolved in after heating or dispersed and suspended in water at ambient temperature to prepare about a 0.1-2 wt. % aqueous solution of gellan gum. An alkaline earth metal salt and/or alkaline metal salt and/or an acidic substance, such as organic or inorganic acid, and acid salts are disclosed to induce gellation at ambient temperature. The utility is said to be foods, medicines, industrial chemicals, etc.

United States Patent No. 5,342,626, which issued to Philip E. Winston Jr., et al. on August 30, 1994 discloses "Composition and Process for Gelatin-Free Soft Capsules", and relates to a polymer composition comprised of gellan, carrageenan and mannan gums and a process for producing flexible films for encapsulation comprising the gellan, carrageenan and mannan gum composition. Such films reportedly can be used for the production of capsules or microcapsules. Capsules are believed to be characterized by a dry outer phase (film membrane) containing a different liquid or solid ingredient in the inner phase.

U.S. Patent 4,857,331 which issued to James J. Shaw et al on August. 15, 1989, discloses pectin/algin/gelatin self standing gels requiring a structuring agent to increase gel strength and in particular this patent also discloses a sugarless ingestible gel confectionery delivery system which includes a pectin gel component, an algin gel component and a polymer network gel component in amounts sufficient to form a gel confectionery unit. The delivery system may also include a further active ingredient such as a drug, medicament, or nutritional supplement.

However, the industry has continued to recognize the need for an improved method of providing compliance with the delivery of drugs to patients which is provided by this invention.

OBJECTS OF THE INVENTION

It is an object of the invention to provide a novel system and a method as a utility for effectively delivering a known effective amount of medication such as a unit amount, to patients who are unable to tolerate presently available medication delivery systems and methods.

Yet another object of this invention is to administer a pharmaceutical preparation which is nonsticky, palatable, easy-to-swallow , or easy to breakdown if need be, of a unit dose, to persons of all ages (e.g., pediatric or geriatric patients) and to animals thus achieving compliance with the desired medication.

It is another object of the invention to provide an effective medication delivery system for those whose cannot tolerate medication containing pastilles, tablets, capsules, trouches, lollipops and chewing gum and the like.

It is yet another object of the invention to provide a useful method for delivering medication to persons who have difficulty in swallowing.

Another objection of this invention is to provide a gel easy to break if desired for mixing with food or producing smaller pieces easy to swallow for humans and animals.

Still another object of this invention is to provide an intact lubricious gel easy to administer for oral, and/or vaginal and/or rectal applications.

It is an additional object of this invention to provide an effective medication delivery system for animals.

These and other objects are met in the invention which is hereinafter described more particularly in detail.

BRIEF SUMMARY OF THE INVENTION

This invention comprises a self-standing (intact) lubricious gel and a process for the production of a self-standing (intact), lubricious gel containing an effective known amount of a biologically-active (medicinal) ingredient for subsequent effective providing to and release in a human or animal biological system of a therapeutic amount of a biologically-active medicinal ingredient whereby the biologically active ingredient is delivered to the biological systems of the patient for effective medical relief to the patient. These lubricious self standing gels can be used for any one of oral, vaginal or rectal administration. The product and method of the present invention also includes a composition in which the gel delivery system can be molded directly in or shaped to accommodate the receptacle which is used to dispense and provide the medication unit to the consumer.

The process for preparation of the gels of this invention comprises admixing gellan gum with water to a concentration from about 0.05% to about 5% and preferably from about 0.25% to about 2.5% by weight of said gum to form a gum containing composition, with or without a sequestrant, and maintaining said gum composition at a temperature sufficiently warm to achieve hydration of said gum in a warm solution such that gelation will occur upon subsequent cooling and admixing a known amount of biologically-active medicinal ingredient with said warm solution and optionally admixing therewith solubilizing and suspending aids and optionally admixing therewith cations and thereafter cooling said warm solution containing said biologically-active ingredient to a temperature in the range sufficient to induce gelation in molds of desired shapes whereby said self-standing (intact) lubricious gel is formed containing a known amount of active.

DETAILED DESCRIPTION OF THE INVENTION

This invention comprises a process for the production of an self-standing (intact) lubricious gel containing an effective known amount of a biologically-active ingredient for subsequent release in a human or animal biological system which comprises admixing gellan gum with water to a concentration from about 0.05% to about 5% and preferably from about 0.25% to about 2.5% by weight of said gum to form a gum containing composition, with or without a sequestrant, and maintaining said gum composition at a temperature sufficiently warm to achieve hydration of said gum such that gelation will occur upon subsequent cooling and admixing a biologically-active ingredient with said warm solution and optionally admixing therewith solubilizing and suspending aids (for the biologically active ingredient, i.e. the drug) and optionally admixing therewith other polymers or additives if desired to alter gel strength or release characteristics and optionally admixing therewith cations and thereafter cooling said warm solution containing said biologically-active ingredient to a temperature in the range sufficient to induce gelation whereby said self-standing (intact) lubricious gel is formed.

As employed herein, the term "self-standing" includes but is not limited to a gel or gels which are capable of standing or staying in an erect mode and are generally not pourable or flowable.

As employed herein, the term "lubricious" includes but is not limited to a gel which has a moist, substantially moist (wet) or partially moist surface at or near surface such that the gel has the feel of a wet surface to the patient (or handfeel for suppositories).

Gellan Gum is a known naturally occurring polysaccharide that is produced by inoculating a carefully formulated fermentation medium with the microorganism *Sphingomonas elodea* (ATTC 31461). *Gellan Gum* is available in clarified forms (*KELCOGEL*®) and (GELRITE®) available from Monsanto Company, U.S.A. The gelling mechanism of *Gellan Gum* is based on cation-induced macromolecular chain association. As employed herein, the term Gellan gum includes non-clarified, clarified, and partially-clarified, native, deacylated and partially deacylated forms as well as mixtures thereof. Useful Gellan Gum(s) include those available commercially but are not limited to those which are sold commercially by Monsanto Company, 800 North Lindbergh Blvd., St. Louis, Missouri, 63167, U.S.A. Processes for preparing gellan gum include those described in U.S. Patents Nos 4,326,052 and 4,236, 053 to Kang both of which are incorporated herein by reference in their entirety.

The process of preparing a gel composition of this invention is preferably carried out at a temperature in step 1 (a) from about 50°C to about 100°C and maintained at that temperature or near that temperature until the gum hydrates or substantially hydrates. Alternatively, hydration can be achieved at room temperature in the presence of appropriate sequestrants. The hydration process is carried out until complete or substantially complete which is when the gum is fully or nearly or sufficiently hydrated, usually resulting in a clear or substantially clear solution.

The process of admixing the biologically-active medicinal ingredient above is typically carried out at a temperature above the gel setting point for a time as it necessary to effectively solubilize or suspend said biologically-active ingredient. Thus the biologically active ingredient is within or in the gel.

If desired other polymers (organic or natural) or additives can be added to the composition to alter texture and/or release characteristics of the gels. Such polymers include but are not limited to one or more of the following, xanthan gum, cellulose derivatives, carrageenan, glucan, curdlan, agar, gelatin, alginates, starch, pectin, blends of xanthan gum with galactomannans and/or glucomannans, mixtures thereof and the like.

An illustrative xanthan gum which may be employed herein include xanthan gum(s) which is(are) sold and registered trademark(s) owned by Monsanto Company, 800 North Lindbergh Blvd, St. Louis, Missouri, 63167 U.S.A. Xanthan gum is an exocellular heteropolysaccharide typically produced by a fermentation process from the bacterium Xanthomonas campestris.

If desired, suitable sequestrants which may be employed herein include sodium citrate, sodium hexametaphosphate (SHMP), disodium phosphate, mixtures thereof and the like. The amount of sequestrant employed may be about 0.05 wt.% to about 0.5 wt.%. Greater and lesser amounts of sequestrant may be employed if desired.

Preferred range for additional optimal cation use level herein is in general from about 0.5 to about 500 mM, or about (0.5 to about 15 mM for divalent cations and about 10 to about 500 mM for monovalent cations for example).

If desired solubilizing aids (which without being bound by theory are believed to help solubilize the biologically active ingredient(s)) maybe employed and preferably selected from the group consisting of ionic or nonionic surfactants and cyclodextrins, mixtures thereof and the like. In an embodiment wherein cations are employed with the process of this invention those preferred cations are those selected from the group consisting of alkali metals, alkaline earth metals and ammonium. In another embodiment of the invention, it is preferred that the cations used are part of the biologically active ingredient if desired. The amount of any solubilizing aid employed depends on the application. This can range from about 0.1% to about 50% or more.

The biologically-active ingredient is not limited and includes but is not limited to a biologically active ingredient(s) which provide(s) therapeutic and/or medicinal and/or pharmacological value to a recipient either by itself of through an active metabolite and/or active derivative. The biologically active ingredient includes any ingredient(s) or similar ingredient which provide such or similar value in whole or part, initially or later, directly or indirectly as through active metabolites or active derivatives of any kind, in whole or in part, mixtures thereof, to a recipient.

The biologically active ingredient is preferably (but not limited to) one or more selected from the group consisting of nutritional supplements (e.g., vitamins, minerals, mineral supplements, plant extracts, amino acids, electrolytes, and proteins), anti-inflammatory (e.g., NSAIDS such as ibuprofen, ketoprofen, fenoprofen, indomethacin, meclofentamate, mefenamic acid, naproxen, phenylbutazone, piroxicam, tolmetin, sulindac, and dimethyl sulfoxide), analgesics, antipyretics, anesthetics including benzocaine, pramoxine, dibucaine, diclonine, lidocaine, mepiracaine, prilocaine, and tetracaine; demulcents (including benzoin, acacia, tragacanth, polyvinyl alcohol and glycerin); analgesics including opiate analgesics (e.g., codeine or hydrocodone), non-opiate analgesics, (e.g., meperidine or methadone), non-narcotic analgesics including acetaminophen and astringent including calamine, zinc oxide, tannic acid, Hamamelis water, zinc sulfate; (e.g., benzalkonium chloride, carbamate peroxide, tannic acid, salicylic acid triclosan, benzoyl peroxide, and boric acid); natural or synthetic steroids including triamcinolone, acetonide, perdnisone, beclomethasone dipropionate; asthmatic drugs including terbutaline sulfate, albuterol, leukotriene receptor antagonists; electrolytes, metals and minerals; antiaxiety and antidepressant agents; antimicrobial and antiviral agents (e.g., acyclovir, neomycin, bacitracin, polymyxin B, vidarabine, trifluridine, zidovucine, methenamine, nonoxynol sulfonamides and other antibiotics); (e.g., fish oils, shark liver oil, castor oil, sucralfate and liver yeast cell derivatives); antihistamines and respiratory agents (e.g., diphenhydramine, promethazine, cromolyn, cyproheptadine and azatadine); immune-suppression agents; cholesterol-lowering agents; cardiac and high-blood pressure agents, cardiovascular and diuretic, hormone, protein, and enzyme active agents, anti neopolastics, gastrointestinal agents, adriamycin, theophylline, ampicillin, amoxicillin, tetracycline and erthromycin and

mixtures thereof and the like. Mixtures of any one or more than one of any of these and any acceptable ingredients may be employed.

Illustrative but non limiting examples of useful biologically active ingredients which may be employed herein include those without limit as recited in American society of Health-System Pharmacists, 1997, [AFHS Drug Information 97] Edited by Gerald K. McEvoy, Bethesda, MD; American Society of Health-System Pharmacists which is incorporated herein in its entirety by reference. Illustrative non limiting examples of useful biologically active ingredients herein also include those without limit as disclosed in Hardman, G.G; [Goodman & Gilman's The Pharmacological basis of Therapeutics], 9th Edition, 1996; New York; McGraw-Hill, Health Professions Division which is also incorporated herein by reference in its entirety. After reading this specification including the Examples those of skill in the art will recognize that a wide range of such biologically active ingredients may be employed in the practice of this invention.

A nonlimiting example of a useful biologically-active ingredient is a nutritional supplement and a nonlimiting example thereof is a vitamin. Vitamin C may be employed herein as a vitamin in the practice of this invention. Potassium chloride is a nonlimiting example of a mineral useful herein.

Other nonlimiting useful biologically-active ingredients include sodium naproxen, sodium salicylate and ibuprofen, mixtures thereof and the like. Additional nonlimiting examples are shown in the Table page 16.

A therapeutically effective amount of a biologically active ingredient is preferably employed in the gel(s) of this invention.

Typically the amount of biologically active ingredient employed in each gel is that amount which is deemed therapeutically effective for the use etc and is also that amount which the gel will handle. Greater and lesser loadings of active ingredient in the gel(s) may be employed if desired. Typically for sodium naproxen, one may be employ from about 50mg/ml. to about 125mg/ml (mg of active / ml of gel (see examples). Greater and lesser amounts may be employed if desired depending on

the use, drug, and other factors. Unit or partial unit dosages may be employed in one or more gels in practicing this invention.

The gel composition(s) of this invention may be conveniently molded or shaped into various shape(s) or mixtures of shapes which are not critical. Preferred shapes are those which are pleasing to patients and of a size and form and shape that is desirable to and swallowable or easy to administer for rectal and vaginal administration to and by the patient or with assistance.

Illustratively, the composition is poured into a suitable mold where the gelation occurs, resulting in a molded composition accepting the shape of the mold and suitable for the patient. Compositions of this invention may then be removed from the mold and administered to patients and animals. Administration can be orally, vaginally and rectally via suppository with or without an applicator assist. The method of administering compositions of this invention is carried out by the patient, an assistant assisting the patient or a combination thereof. The shape, texture (hardness of gel), amount of ingredient, size and other features of the gel will be adjusted by those of skill in the art depending on the administration, patient, patient age and conditions, doctor preferences, drug employed and many other factors depending on the use.

The biologically-active ingredient(s) employed in this invention includes both water soluble and water insoluble biologically-active ingredients without limit. An effective (therapeutic) amount of biologically-active ingredient is preferably employed. The effective (therapeutic) amount of such ingredient will be that amount which is effective for the recipient patient who is receiving medication in the practice of this invention and is typically that which is recited on the label of the medication or prescribed by a medical doctor or veterinarian. Delivery hereunder is achieved in an effective manner and time and takes into account the patient, the drug, and the ability of the patient to be receptive to the manner of delivery of and the ingredient, among many factors.

The patient may swallow or otherwise consume (e.g. rectal and vaginal administration) the gel composition of this invention comprising at least one

biologically-active ingredient. The medication is thus provided to the patient internally and thus made available to the patient's gastrointestinal tract or other areas for beneficial use by the patient as for example when taken orally. The administration of gels via vaginal and rectal administration will be apparent to those of skill in the art following known procedures for administering gels via vaginal and rectal (suppository) administration with and without applicator assist.

In another embodiment, this invention comprises a method employed by a patient of easing the swallowing of a biologically-active ingredient which comprises administering a gel prepared by the process of this invention to a human or animal. Illustrative animals which may be given and provided effectively gels of this invention include cats, dogs, horses, sheep, fish, swine, cattle and the like. One or more gels of this invention may be administered and taken at a time to provide an effective and safe amount of medication during consumption.

In another embodiment, this invention comprises a method for a patient to ease breaking a gel and mixing it with food for humans and animals. The gel of this invention can be made easy to break, if need be, and can be mixed with food or produce smaller entities easier to swallow by a human.

In another embodiment, this invention comprises a method to ease vaginal or rectal administration of a lubricious gel of this invention. The texture of the gel(s) of this invention may be modified appreciably depending on the method of administration contemplated and the recipient desired.

The shape can be molded into those shapes which are aesthetically pleasing if desired or color coded or marked to provide increased compliance measures. The shape and texture of the gel can also be configured and texturized to provide such increased compliance measures. For example, the mold could contain the name of drug dosage, form, etc.

EXAMPLES

The examples produced herein are only illustrations of various embodiments of this invention and are not intended to limit it in any way.

Example 1

Preparation of Na-Naproxen Gellan Gels

A 0.5% solution of GELRITE® gelling agent (GELRITE® is a registered trademark of Monsanto Company, 800 North Lindbergh Blvd., St. Louis, Missouri, 63167, U.S.A. in distilled water is prepared by adding 0.125 g of GELRITE® to 25 milliliters of distilled water with agitation from a stir bar. The GELRITE® solution is heated to 90-95 °C for 3-5 minutes to hydrate the GELRITE® Gum and produce a clear solution. The GELRITE® gelling agent is cooled to about 75 -78 °C and mixed with 2.5 g of Na-Naproxen until the drug is completely dissolved. This produces a drug concentration of 100 mg/ml of solution. The warm drug solution is poured into molds and allowed to cool. Solutions gel as the temperature drops below 40° C and forms free-standing (intact) lubricious gels, easy to mold gel containing sodium naproxen illustrative of a biologically active ingredient. (Na-naproxen is an approved medication which is sold over the counter as an anti-inflammatory medicine.) This produced a gel containing a biologically active ingredient illustrative of this invention. For example when 2ml solution were poured in mold, final gels contained 200 mg sodium naproxen.

The following examples were prepared following the general procedure in Example 1.

Example Number	GELRITE® Solution Concentration	Na-Naproxen Concentration	Resulting dose of naproxen in 2ml gels
2	0.25 %	125 mg/mL	250 mg
3	0.50 %	125 mg/mL	250 mg
4	0.50 %	62 mg/mL	124 mg
5	1.00 %	125 mg/mL	250 mg
6	1.00 %	62 mg/mL	124 mg
7	0.50 %	100 mg/mL	200 mg

Examples 8-20

Various biologically-active materials (Na-Naproxen, ascorbic acid, ibuprofen, penicillin etc.) were incorporated into the Gelrite® gelling agent to illustrate preparing a gel of this invention. In all cases, the preparation of the gel containing an illustrative biologically active ingredient in these Examples followed the procedure described in Example 1. Hardnesses were measured on an Instron Model 4201. Data is given in lbs. which represent the rupture point of the gels under test in the Instron. (Instron Test Instrument Model 4201, Instron, 100 Royale Street, Canton, Massachusetts, 02021, U.S.A.) The rupture point was measured to show the gels of this invention are free standing and can be broken in smaller pieces if needed.

Example	Initial GELRITE® Concentration	Biologically-Active Material	Active Concentration	Hardness (lbs.)
*7**	*0.50%*	*Na-Naproxen*	*100 mg/mL*	*2.1*
8	0.50%	Potassium Chloride	25 mg/mL	1.8
9	0.75%	Potassium Chloride	25 mg/mL	4.3
10	1.00%	Potassium Chloride	25 mg/mL	5.2
11	0.50%	Iron Sulfate	100 mg/mL	1.4
12	0.75%	Iron Sulfate	100 mg/mL	2.4
13	1.00%	Iron Sulfate	100 mg/mL	3.0
14	0.50%	Ascorbic Acid	250 mg/mL	1.0
15	0.75%	Ascorbic Acid	250 mg/mL	1.7
16	1.00%	Ascorbic Acid	250 mg/mL	2.7
17	0.75%	Ibuprofen	75 mg/mL	2.1
18	0.25%	Ibuprofen	150 mg/mL	0.96
19	0.50%	Penicillin G	100 mg/mL	1.2
20	0.75%	Penicillin G	250 mg/mL	1.3
21	1.00%	Penicillin G	250 mg/mL	1.8

* Same as previous page (with hardness given)

Other Examples 22-27 below were prepared as previously described, by adding calcium chloride to the warm solution, so that the overall calcium concentration in the gel was 6mM.

Example	Initial GELRITE® Concentration	Biologically-Active Material	Active Concentration	Hardness *(lbs.)*
22	0.75	Pseudoephedrine HCl	30 mg/mL	4.26
23	0.75	Phenylpropanolamine HCl	12.5 mg/mL	4.29
24	0.75	Chlorpherinamine	2 mg/mL	5.06
25	0.75	Bromopheniramine	2 mg/mL	5.85
26	0.75	Dextrometorphan	5 mg/mL	5.08
27	0.75	Diphenhydramine HCl	12.5 mg/mL	4.73
28	0.75	Acetaminophen	100 mg/mL	5.42

By comparison, commercially available soft-gels (e.g., Pfizer® Unisom Sleepgels) Registered trademark Pfizer, Inc., distributed by Consumer Health Care Group, Pfizer, Inc., New York, NY, 10017 U.S.A. or Gelcaps (Vons® Liquid-Gelcaps) Cough & cold Liquid Liquid-Gelcaps, The Von Companies, Inc., P.O. Box 3338, Los Angeles, CA 90051, U.S.A. could not be ruptured in the Instron (e.g., force limit is 100 lbs.)

Thus, it is apparent that there has been provided, in accordance with the instant invention, a novel composition, drug delivery system, a process and a method(s) for easing the swallowing and/or administration of pharmaceutically active drug(s) or metabolites or derivatives or medicine that fully satisfies the objects and advantages set forth herein above. While the invention has been described with respect to various specific examples and embodiments thereof, it is understood that the invention is not limited thereto and many alternatives, modifications and variations will be apparent to those skilled in the art in light of the foregoing description. Accordingly, it is intended to embrace all such alternatives, modifications and variations as fall within the spirit and broad scope of the invention.

CLAIM OR CLAIMS

WHAT IS CLAIMED IS:

1. A process for preparing a self-standing (intact) lubricious gel containing a therapeutic amount of a biologically-active ingredient, for subsequent providing and/or effective release of said active ingredient, or an active derivative or active metabolite, to or in a human or animal biological system which comprises:

a. admixing gellan gum with water to form a concentration from about 0.05% to about 5% by weight of gellan gum, optionally adding sequestrant and polymers/additives, and maintaining said composition at a temperature sufficiently warm to achieve such hydration of gellan gum such that gelation will occur upon subsequent cooling in a desired (appropriate) mold;

b. admixing said biologically-active ingredient with said warm solution and optionally admixing therewith suitable solubilizing and suspending aids and optionally admixing therewith suitable cation(s) and;

c. cooling said warm solution containing said biologically-active ingredient to a temperature sufficient to induce gelation whereby said intact lubricious gel is formed.

2. The process of Claim 1 wherein said temperature of step 1 (a) is from about 20 ^{0}C to about 100^{0}C and is maintained at or near that temperature until said gum hydrates.

3. The process of Claim 1 wherein said warm solution preparing in Step 1 (b) is maintained at a temperature of about 35^0 C to about 85^0 C for a time necessary to substantially solubilize or suspend said biologically-active ingredient.

4. The process of Claim 1 wherein the cation used to induce gelation of the gel is or has been provided by in whole or in part or is or has been a part of said biologically active ingredient.

5. The process of Claim 1 wherein said drug solubilizing aids are employed and can be selected from the group consisting of ionic or nonionic surfactants and cyclodextrins or mixtures thereof.

6. The process of Claim 1 wherein said cations are supplied from an external source, and are employed in Step 1 (b).

7. The process of Claim 5 wherein said cations are selected from the group consisting of alkali metals, alkaline earth metals, ammonium and mixtures thereof.

8. The process of claim 1, wherein said biologically-active ingredient is selected from the group consisting of nutritional supplements, amino acids, electrolytes, proteins, anti-inflammatory (e.g., NSAIDS (non-steroidal anti-inflammatory drugs) such as s-ibuprofen, ketoprofen, fenoprofen, indomethacin, meclofentamate, mefenamic acid, naproxen, phenylbutazone, piroxicam, tolmetin, sulindac, and dimethyl sulfoxide), analgesics, antipyretics, anesthetics including benzocaine, pramoxine, dibucaine, diclonine, lidocaine, mepiracaine, prilocaine, and tetracaine; demulcents; analgesics including opiate analgesics, non-opiate analgesics, non-narcotic analgesics including acetaminophen and astringent including calamine, zinc oxide, tannic acid, Hamamelis water, zinc sulfate; natural or synthetic steroids including triamcinolone, acetonide, perdnisone, beclomethasone dipropionate; asthmatic drugs including terbutaline sulfate, albuterol, leukotriene receptor anatagonists; electrolytes, metals and minerals; antiaxiety and antidepressant agents; antimicrobial and antiviral agents; antihistamines; immune-suppression agents; cholesterol-lowering agents; cardiac, high-blood pressure agents, CNS (central nervous system) stimulants, anti convulsants, muscle relaxants, psychotherapeutic agents, cardiovascular, diuretics, hormones, protein and enzymatic agents, antineoplastic, gastrointestinal and respiratory agents, and mixtures thereof.

9. The process of Claim 2 wherein said nutritional supplement is a vitamin.

10. The process of Claim 3 wherein said vitamin is Vitamin C.

11. The process of Claim 2 wherein said active ingredient is sodium naproxen or ibuprofen.

12. The process of Claim 2 wherein said active ingredient is sodium salicylate.

13. A self-standing (intact), self-lubricating gel composition which comprises an intact lubricious gel containing and/or providing a therapeutic amount of a biologically-active ingredient or metabolite or derivative for subsequent providing to and release in a human or animal biological system which further comprises gellan gum, water and a biologically-active ingredient.

14. The gel of claim 13, wherein said biologically-active ingredient is selected from the group consisting of nutritional supplements, anti-inflammatory (e.g., NSAIDS such as s-ibuprofen, ketoprofen, fenoprofen, indomethacin, meclofentamate, mefenamic acid, naproxen, phenylbutazone, piroxicam, tolmetin, sulindac, and dimethyl sulfoxide), analgesics, antipyretics, anesthetics including benzocaine, pramoxine, dibucaine, diclonine, lidocaine, mepiracaine, prilocaine, and tetracaine; demulcents; analgesics including opiate analgesics, non-opiate analgesics, non-narcotic analgesics including acetaminophen and astringent including calamine, zinc oxide, tannic acid, Hamamelis water, zinc sulfate; natural or synthetic steroids including triamcinolone, acetonide, perdnisone, beclomethasone dipropionate; asthmatic drugs including terbutaline sulfate, albuterol, leukotriene receptor anatagonists; electrolytes, metals and minerals; antiaxiety and antidepressant agents; antimicrobial and antiviral agents; antihistamines; immune-suppression agents; cholesterol-lowering agents; cardiac, high-blood pressure agents, CNS (central nervous system) stimulants, anti convulsants, muscle relaxants, psychotherapeutic agents, cardiovascular, diuretics, hormones, protein and enzymatic agents, antineoplastic, gastrointestinal and respiratory agents, and mixtures thereof

15. The gel of Claim 14 wherein said nutritional supplement is a vitamin.

16. The gel of Claim 14 wherein said vitamin is Vitamin C.

17. The gel of Claim 14 wherein said active ingredient is sodium naproxen or ibuprofen.

18. The gel of Claim 14 wherein said active ingredient is sodium salicylate.

19. A drug delivery system which comprises an intact lubricious gel containing a therapeutic amount of a biologically-active (medicinal) ingredient for subsequent release in a human or animal biological system which further comprises gellan gum and a biologically-active medicinal ingredient.

20. The drug delivery system of claim 19, wherein said biologically-active ingredient is selected from the group consisting of nutritional supplements, anti-inflammatory (e.g., NSAIDS such as ibuprofen, ketoprofen, fenoprofen, indomethacin, meclofentamate, mefenamic acid, naproxen, phenylbutazone, piroxicam, tolmetin, sulindac, and dimethyl sulfoxide), analgesics, antipyretics, anesthetics including benzocaine, pramoxine, dibucaine, diclonine, lidocaine, mepiracaine, prilocaine, and tetracaine; demulcents; analgesics including opiate analgesics, non-opiate analgesics, non-narcotic analgesics including acetaminophen and astringent including calamine, zinc oxide, tannic acid, Hamamelis water, zinc sulfate; natural or synthetic steroids including triamcinolone, acetonide, perdnisone, beclomethasone dipropionate; asthmatic drugs including terbutaline sulfate, albuterol, leukotriene receptor anatagonists; electrolytes, metals and minerals; antiaxiety and antidepressant agents; antimicrobial and antiviral agents; antihistamines; immune-suppression agents; cholesterol-lowering agents; cardiac, high-blood pressure agents, CNS (central nervous system) stimulants, anti convulsants, muscle relaxants, psychotherapeutic agents, cardiovascular, diuretics, hormones, protein and enzymatic agents, antineoplastic, gastrointestinal and respiratory agents, and mixtures thereof.

21. The drug delivery system of Claim 20 wherein said nutritional supplement is a vitamin.

22. The drug delivery system of Claim 20 wherein said vitamin is Vitamin C.

23. The drug delivery system of Claim 21 wherein said active ingredient is sodium naproxen or ibuprofen.

24. The drug delivery system of Claim 21 wherein said active ingredient is sodium salicylate.

25. A method of easing the swallowing by a human or animal of a biologically-active ingredient which comprises administering an intact gel or a broken or reduced size gel, optionally mixed with food, comprising gellan gum and a biologically active medicinal ingredient to said human or animal.

26. The method of claim 25, wherein said biologically-active ingredient is selected from the group consisting of nutritional supplements, anti-inflammatory (e.g., NSAIDS such as ibuprofen, ketoprofen, fenoprofen, indomethacin, meclofentamate, mefenamic acid, naproxen, phenylbutazone, piroxicam, tolmetin, sulindac, and dimethyl sulfoxide), analgesics, antipyretics, anesthetics including benzocaine, pramoxine, dibucaine, diclonine, lidocaine, mepiracaine, prilocaine, and tetracaine; demulcents; analgesics including opiate analgesics, non-opiate analgesics, non-narcotic analgesics including acetaminophen and astringent including calamine, zinc oxide, tannic acid, Hamamelis water, zinc sulfate; natural or synthetic steroids including triamcinolone, acetonide, perdnisone, beclomethasone dipropionate; asthmatic drugs including terbutaline sulfate, albuterol, leukotriene receptor anatagonists; electrolytes, metals and minerals; antiaxiety and antidepressant agents; antimicrobial and antiviral agents; antihistamines; immune-suppression agents; cholesterol-lowering agents; cardiac, high-blood pressure agents, CNS (central nervous system) stimulants, anti convulsants, muscle relaxants, psychotherapeutic agents, cardiovascular, diuretics, hormones, protein and enzymatic agents, antineoplastic, gastrointestinal and respiratory agents, and mixtures thereof

27. The method of Claim 25 wherein said nutritional supplement is a vitamin.

28. The method of Claim 25 wherein said vitamin is Vitamin C.

29. The method of Claim 25 wherein said active ingredient is sodium naproxen or ibuprofen.

30. The method of Claim 25 wherein said active ingredient is sodium salicylate.

31. A method of easing the vaginal administration and rectal administration to a human or animal of a biologically active ingredient which comprises administering a gel prepared by the process of Claim 1 to said human or animal.

32. The method of claim 31, wherein said biologically-active ingredient is selected from the group consisting of nutritional supplements, anti-inflammatory (e.g., NSAIDS such as ibuprofen, ketoprofen, fenoprofen, indomethacin, meclofentamate, mefenamic acid, naproxen, phenylbutazone, piroxicam, tolmetin, sulindac, and dimethyl sulfoxide), analgesics, antipyretics, anesthetics including benzocaine, pramoxine, dibucaine, diclonine, lidocaine, mepiracaine, prilocaine, and tetracaine; demulcents; analgesics including opiate analgesics, non-opiate analgesics, non-narcotic analgesics including acetaminophen and astringent including calamine, zinc oxide, tannic acid, Hamamelis water, zinc sulfate; natural or synthetic steroids including triamcinolone, acetonide, perdnisone, beclomethasone dipropionate; asthmatic drugs including terbutaline sulfate, albuterol, leukotriene receptor anatagonists; electrolytes, metals and minerals; antiaxiety and antidepressant agents; antimicrobial and antiviral agents; antihistamines; immune-suppression agents; cholesterol-lowering agents; cardiac, high-blood pressure agents, CNS (central nervous system) stimulants, anti convulsants, muscle relaxants, psychotherapeutic agents, cardiovascular, diuretics, hormones, protein and enzymatic agents, antineoplastic, gastrointestinal and respiratory agents, and mixtures thereof.

33. The method of Claim 31 wherein said nutritional supplement is a vitamin.

34. The method of Claim 31 wherein said vitamin is Vitamin C.

35. The method of Claim 31 wherein said active ingredient is sodium naproxen or ibuprofen.

36. The method of Claim 31 wherein said active ingredient is sodium salicylate.

INTERNATIONAL SEARCH REPORT

Inter ·al Application No
PCT/US 97/21408

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/36 A61K9/06 A61K31/19 A61K31/375

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BHAKOO, M.; WOERLY, S.; DUNCAN, R.: "Release of antibiotics and antitumour agents from alginate and gellan gum gels" PROCEEDINGS OF THE INTERNATIONAL SYMPOSIUM ON CONTROLLED RELEASE BIOACTIVE MATERIAL, vol. 18, July 1991, AMSTERDAM, pages 441-442, XP002057750 cited in the application	13
A	see page 441, column 1, line 16-20 see page 441, column 2, line 5-8	1
X	PATENT ABSTRACTS OF JAPAN vol. 013, no. 151 (C-584), 12 April 1989 & JP 63 309150 A (SAN EI CHEM IND LTD), 16 December 1988, cited in the application	13
A	see abstract	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

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Date of the actual completion of theinternational search	Date of mailing of the international search report
6 March 1998	18/03/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	La Gaetana, R

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 97/21408

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 011, no. 353 (C-457), 18 November 1987 & JP 62 126943 A (SAN EI CHEM IND LTD), 9 June 1987, cited in the application	13
A	see abstract	1
A	FR 2 720 944 A (SANOFI SA) 15 December 1995 see page 3, line 27-30 see page 4, line 1-15 see page 5, line 28-34	1,13
A	WO 94 27578 A (PHARMACIA AB ;CARLFORS JOHAN (SE); EDSMAN KATARINA (SE)) 8 December 1994 see page 1, line 12-17 see page 3, line 7-24 see page 4, line 26-27	1,13

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/US 97/21408

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		EP 0765156 A	02-04-97
		WO 9533444 A	14-12-95
WO 9427578 A	08-12-94	AU 6940594 A	20-12-94
		CA 2164113 A	08-12-94
		EP 0706372 A	17-04-96
		JP 8510731 T	12-11-96